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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC,
SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA,
UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations
- of inventorship (Rule 4.17(iv)) for US only

Published:

- with international search report

(88) Date of publication of the international search report:
15 July 2004

(15) Information about Correction:

Previous Correction:

see PCT Gazette No. 22/2004 of 27 May 2004, Section II

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: BACTERICIDAL, ANTI-APOPTOTIC, PRO-INFLAMMATORY AND ANTI-INFLAMMATORY PEPTIDES OF HEPARIN-BINDING PROTEIN (HBP) OR HUMAN NEUTROPHIL ELASTASE

(57) Abstract: The present invention relates to providing new peptide fragments derived from the sequence of heparin-binding protein (HBP) and/or human neutrophil elastase and using said fragments for the manufacture of a medicament for the treatment of Gram positive and/or Gram negative infections. Thus, the peptides of the inventions can be used for treatment of pneumonia and meningitis. The peptides of the invention may also be advantageously used for the treatment of any pathological condition demanding modulating of inflammatory response and/or a condition involving sepsis and/or, disseminated intravascular coagulation. Among other pathological conditions, which may be regarded for the treatment with the peptides of the invention, are conditions involving cell apoptosis.

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference P680PC00	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/DK 03/00542	International filing date (day/month/year) 14/08/2003	(Earliest) Priority Date (day/month/year) 15/08/2002
Applicant LEUKOTECH A/S		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 9 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☒ contained in the international application in written form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

**BACTERICIDAL, ANTI-APOPTOTIC, PRO-INFLAMMATORY AND ANTI-INFLAMMATORY PEPTIDES OF
HEPARIN-BINDING PROTEIN (HBP) OR HUMAN NEUTROPHIL ELASTASE**

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ **None of the figures.**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 03/00542

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 67,70
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 67,70

Present claims 67 and 70 relate to an extremely large number of possible peptides. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the peptides claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been focused on those parts of the claims which appear to be supported and disclosed, namely those parts related to the peptides disclosed as SEQ ID NOs 594 (claim 68) and 593 (claim 71) respectively. Thereto, the more general aspects underlying the invention, regarding the use of peptides derived from human HBP and porcine HBP as proinflammatory peptides and anti-inflammatory peptides respectively, have been included in the search.

Regarding claim 68: the definition of SEQ ID NO:594 differs between the sequence listing and the description. The definition of the description has been used in the search.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-73

The present application has been considered to contain several inventions which are not linked such that they form a single general inventive concept, as required by Rules 13.1, 13.2 and 13.3 PCT for the following reasons:

The prior art has been identified as: US6071879 (D1) and Periera et al. "Synthetic bactericidal peptide based on CAP37: A 37-kDa human neutrophil granule-associated cationic antimicrobial protein chemotactic for monocytes, Proceedings of the National Academy of Sciences of the United States of America (1993), 90(10), 4733-7 (D2).

D1 shows the use of a peptide consisting of amino acids 20-44 of CAP37 or effective subunits thereof in the treatment of bacterial infections (activity against gram positive and gram negative bacteria) and septic shock. See SEQ ID NO: 1, col. 6 line 25-col. 7 line 1 and col. 12 lines 40-50.

D2 shows that peptides consisting of amino acids 20-44 of CAP37 or human neutrophil elastase (ELAS) have bactericidal effect. The CAP37-derived peptide shows effect against gram positive as well as gram negative bacteria. See abstract, p. 4734 left column paragraph 3, p. 4736 fig. 5 and left column paragraph 2.

2. Claims: -

Thus, within the group of peptides covered by claims 1-52, previously known peptides are included. The use of such peptides in treatment of bacterial infections or sepsis is also disclosed in prior art.

The special technical feature of each of the peptides that makes a contribution over prior art (Rule 13.2 PCT) is the specific sequence of the peptide. From this special technical feature the objective problem to be solved by this and all further inventions is to provide alternative peptides. Therefore, each of the claimed peptides constitutes one invention.

However, if a group of peptides share the same function (e.g. that they function as proinflammatory peptides or that they function as anti-inflammatory peptides or can be used for the prevention of cell apoptosis), and if this function constitutes a special technical features which make a contribution over the prior art (Rule 13.2 PCT), such peptides can possibly be grouped as one invention according to their use/function. So far, however, no obvious grouping of the peptides could be made given the information disclosed in the description. It is not evident from the

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

description which sequence has which function, and therefore the peptides could not be grouped in a logic way. For example, not all peptides covered by claims 1-53 can be used to inhibit inflammatory response. Thus, so far each of the sequences covered by present claims 1-52 is considered to represent one invention.

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International Application No

PCT/DK 03/00542

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K14/47 C07K2/00 A61K38/17 A61K38/02 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, MEDLINE, BIOSIS, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 071 879 A (PEREIRA HELOISE ANNE) 6 June 2000 (2000-06-06) column 6, line 25 - column 7, line 1 column 12, line 40 - line 50 SEQ ID NO 1 --- -/--	1-63,73

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

1 April 2004

Date of mailing of the international search report

29 APR 2004

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SARA NILSSON / ELY

INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 03/00542

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>PEREIRA H A ET AL: "Synthetic bactericidal peptide based on CAP37: a 37-kDa human neutrophil granule-associated cationic antimicrobial protein chemotactic for monocytes." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA. UNITED STATES 15 MAY 1993, vol. 90, no. 10, 15 May 1993 (1993-05-15), pages 4733-4737, XP002275782 ISSN: 0027-8424 cited in the application page 4734, left-hand column, paragraph 3 page 4736, left-hand column, paragraph 2; figure 5 abstract</p>	1-63,73
X	<p>--- US 5 650 392 A (BRACKETT DANIEL J ET AL) 22 July 1997 (1997-07-22) column 11 -column 12 SEQ ID NO 1</p>	1-63,73
X	<p>--- WO 93 19087 A (UNIV EMORY MED) 30 September 1993 (1993-09-30) page 62, line 17 -page 63, line 16 claims 16,25-27 SEQ ID NO 8</p>	1-63, 66-69,73
X	<p>--- D'CRUZ OSMOND J ET AL: "Sperm immobilizing activity of a synthetic bioactive peptide 20-44 of 37-kDa cationic antimicrobial protein (CAP37) of human neutrophils" JOURNAL OF ANDROLOGY, vol. 16, no. 5, 1995, pages 432-440, XP002275783 ISSN: 0196-3635 abstract</p>	1-58,73
A	<p>--- HEINZELMANN M ET AL: "Heparin binding protein (CAP37) differentially modulates endotoxin-induced cytokine production." INTERNATIONAL JOURNAL OF SURGICAL INVESTIGATION. ENGLAND 2001, vol. 2, no. 6, 2001, pages 457-466, XP002275784 ISSN: 1028-5229 see especially "conslusions" in the abstract</p> <p>--- -/--</p>	64,67-69

INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 03/00542

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 2 May 2002 (2002-05-02) WEINRAUCH YVETTE ET AL: "Neutrophil elastase targets virulence factors of enterobacteria" Database accession no. PREV200200430146 XP002275787 abstract & NATURE (LONDON), vol. 417, no. 6884, 2 May 2002 (2002-05-02), pages 91-94, ISSN: 0028-0836</p> <p>---</p>	1-66,73
A	<p>TAPPER HANS ET AL: "Secretion of heparin-binding protein from human neutrophils is determined by its localization in azurophilic granules and secretory vesicles" BLOOD, vol. 99, no. 5, 1 March 2002 (2002-03-01), pages 1785-1793, XP002275785 ISSN: 0006-4971 page 1786, left-hand column, paragraph 2</p> <p>---</p>	1-73
A	<p>MILIND S. SHROTRI ET AL: "Heparin-binding protein decreases apoptosis in human and murine neutrophils" JOURNAL OF SURGICAL RESEARCH, vol. 89, 2000, pages 53-59, XP002275786 ISSN: 0022-4804 abstract "results" and "conclusions".</p> <p>-----</p>	1-69,73

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/DK 03/00542

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6071879	A	06-06-2000	US 5877151 A	02-03-1999
			US 5627262 A	06-05-1997
			US 5607916 A	04-03-1997
			US 5458874 A	17-10-1995
			US 5484885 A	16-01-1996
			US 5650392 A	22-07-1997
			AU 4808993 A	21-10-1993
			WO 9319087 A1	30-09-1993
			AU 6033690 A	06-02-1991
			WO 9100907 A1	24-01-1991

US 5650392	A	22-07-1997	US 5607916 A	04-03-1997
			US 5458874 A	17-10-1995
			US 5484885 A	16-01-1996
			US 6071879 A	06-06-2000
			US 5627262 A	06-05-1997
			US 5877151 A	02-03-1999
			AU 4808993 A	21-10-1993
			WO 9319087 A1	30-09-1993
			AU 6033690 A	06-02-1991
			WO 9100907 A1	24-01-1991

WO 9319087	A	30-09-1993	US 5484885 A	16-01-1996
			AU 4808993 A	21-10-1993
			WO 9319087 A1	30-09-1993
			US 5607916 A	04-03-1997
			US 6071879 A	06-06-2000
			US 5650392 A	22-07-1997
			US 5627262 A	06-05-1997
			US 5877151 A	02-03-1999
			US 5458874 A	17-10-1995
